

# PMS2 elevation is associated with prostate cancer

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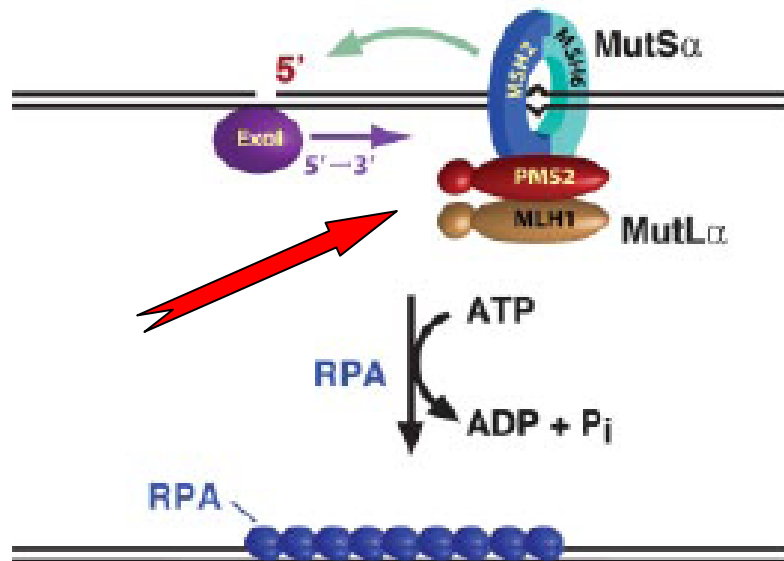
Assistant Professor

Cancer Biology

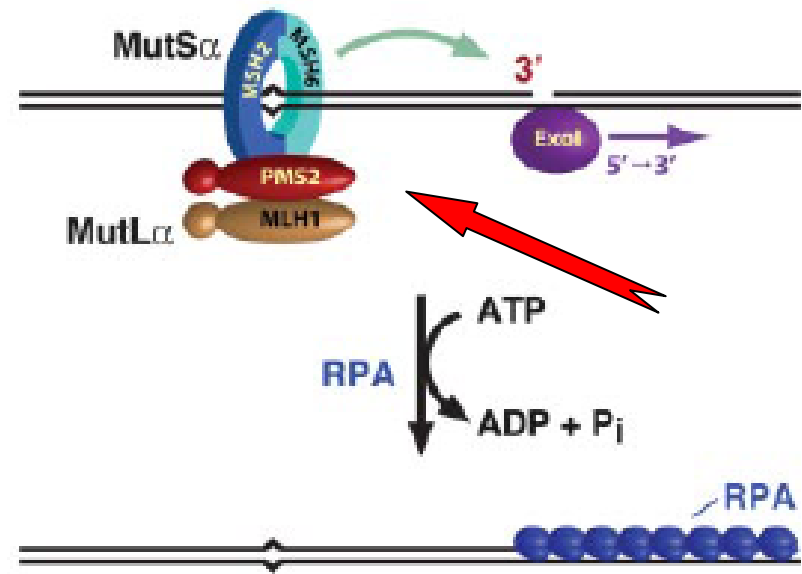
Wake Forest University School of Medicine

# MISMATCH REPAIR

## 5'-heteroduplex:



## 3'-heteroduplex:



- **Loss of mismatch repair proteins** (MSH2, MLH1) is often associated with the predisposition or development of cancer, particularly a hereditary form of colon cancer, HNPCC
- We show that the **elevation of a mismatch repair protein** is significantly associated with a type of cancer that is not part of the HNPCC spectrum: **PROSTATE CANCER**

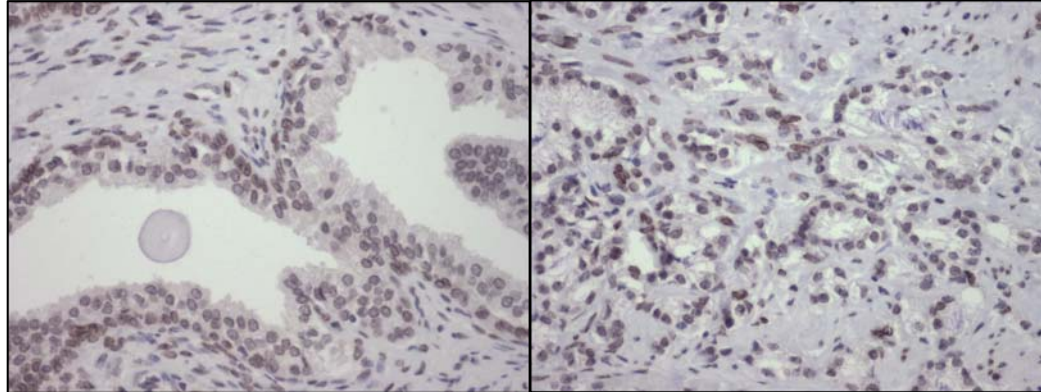
- **Only 25-30% of tumors become aggressive, regardless of previous treatment**
- **Most commonly used prostate cancer cell lines contain defects in at least one MMR protein**
- **MMR defects have been observed in prostate cancer**

# PMS2 and MLH1 in prostate cancer

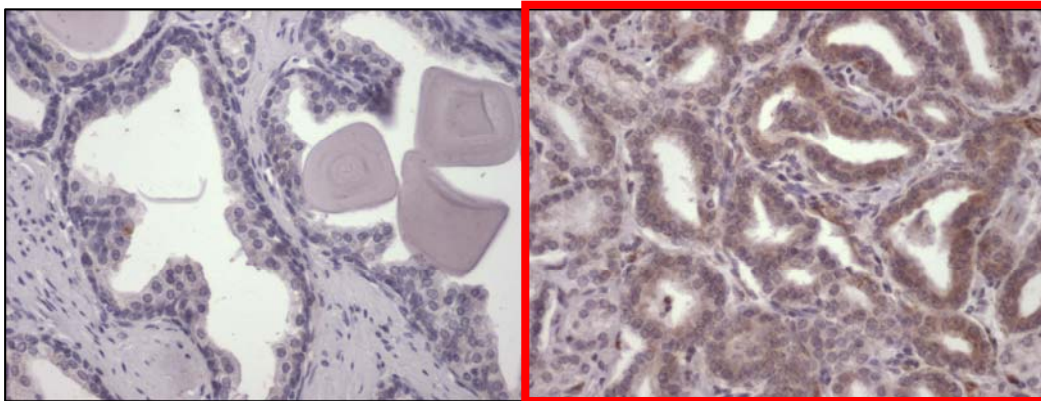
Normal/Benign

Cancer

MLH1

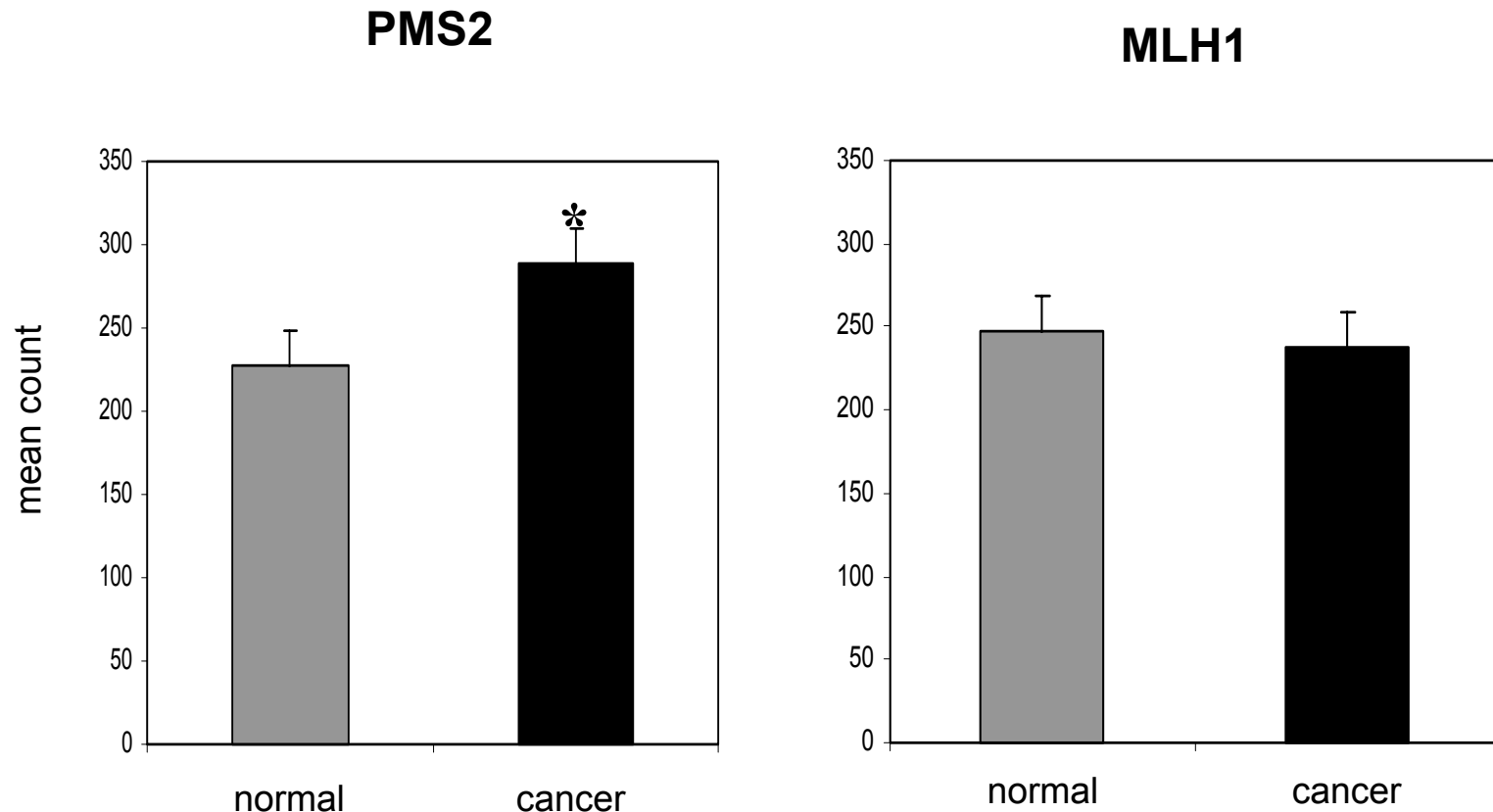


PMS2



A. M. Norris, R. D. Woodruff, R. B. D'Agostino Jr., J. E. Clodfelter & **Karin Drotschmann Scarpinato** (2007). Elevated levels of the mismatch repair protein PMS2 are associated with prostate cancer. *Prostate*, 67, 214-225.

# PMS2 elevation in prostate cancer

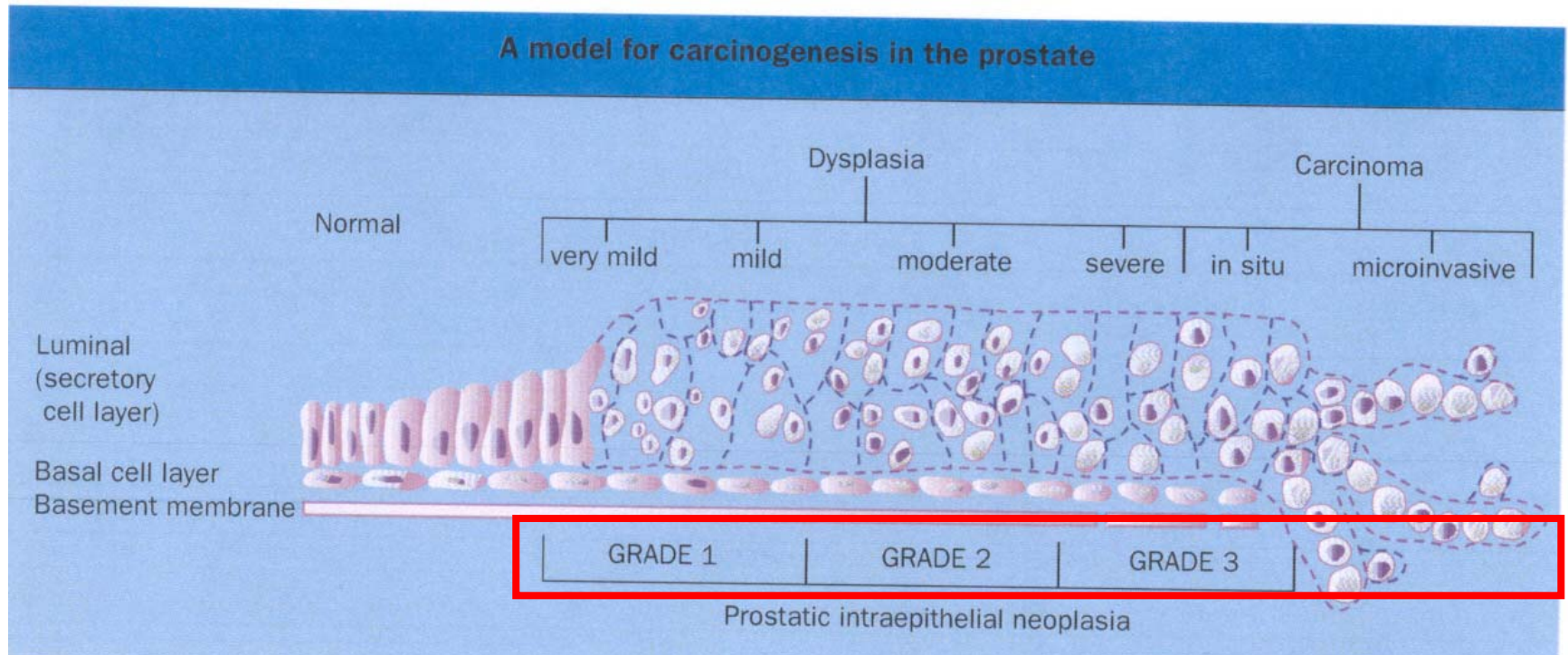


**PMS2 is significantly elevated in prostate cancer,**

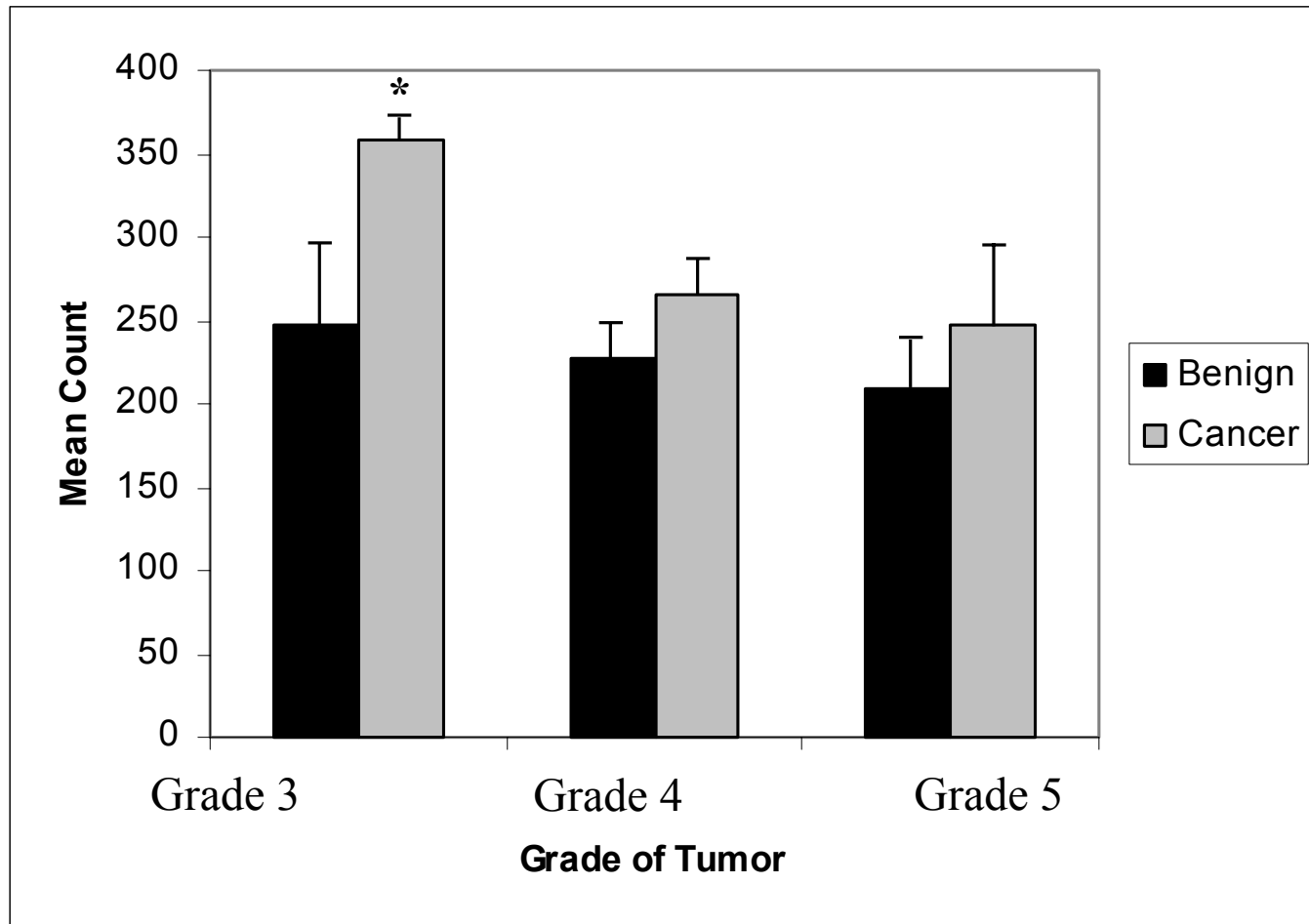
**independent of MLH1**

A. M. Norris, R. D. Woodruff, R. B. D'Agostino Jr., J. E. Clodfelter & Karin Drotschmann Scarpinato (2007). Elevated levels of the mismatch repair protein PMS2 are associated with prostate cancer. *Prostate*, 67, 214-225.

# Prostate Cancer Stages



# PMS2 elevation in tissue of different Gleason grade



A. M. Norris, R. D. Woodruff, R. B. D'Agostino Jr., J. E. Clodfelter & **Karin Drotschmann Scarpinato** (2007). Elevated levels of the mismatch repair protein PMS2 are associated with prostate cancer. *Prostate*, 67, 214-225.



# Statistical analysis of PMS2 elevation in prostate cancer

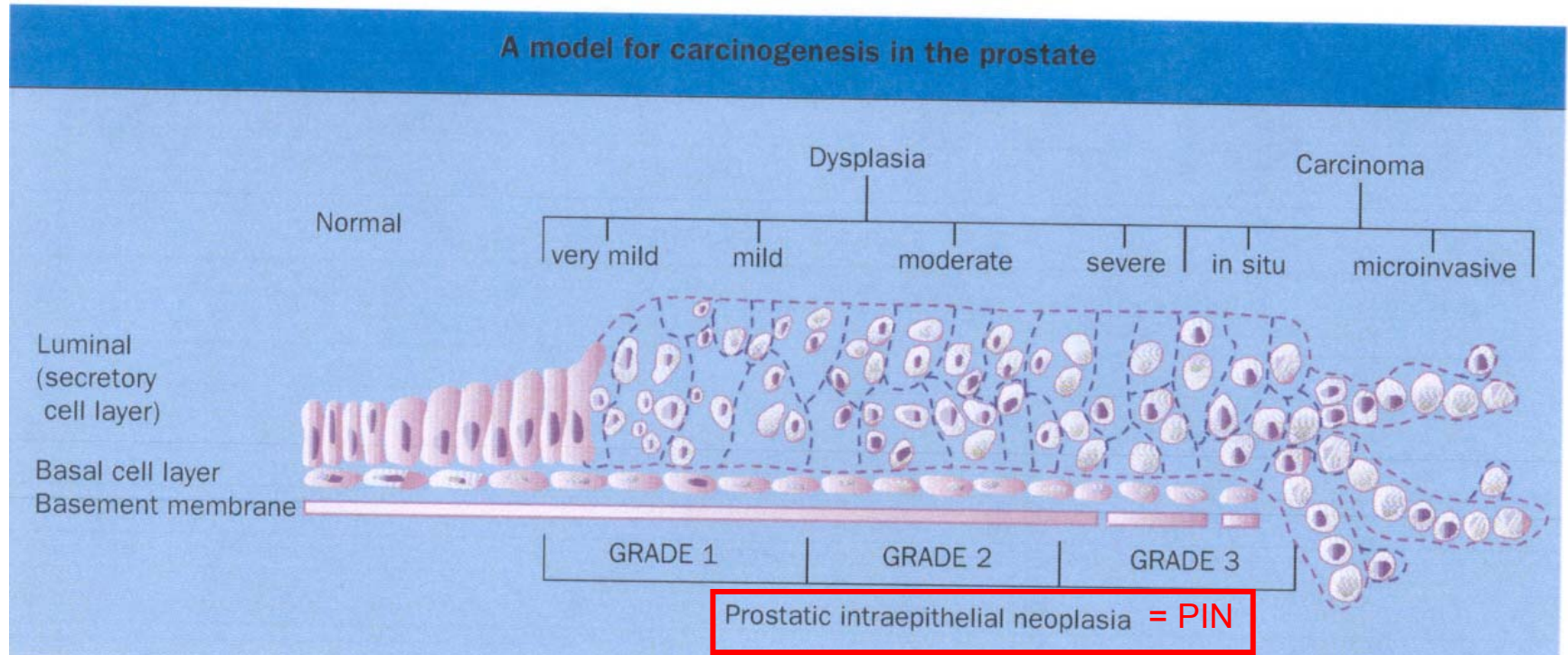
<i>Protein</i>	<i>Comparison between</i>	<i>p-value</i>
MSH2	Normal – Cancer	0.107
	grade 3 – 4	0.74
	grade 3 – 5	0.57
	grade 4 – 5	0.38
MLH1	Normal – Cancer	0.501
<b>PMS2</b>	<b>Normal – Cancer</b>	<b>&lt; 0.0001</b>
	<b>grade 3 – 4 *</b>	<b>0.017</b>
	<b>grade 3 – 5 *</b>	<b>0.019</b>
	grade 4 – 5 *	0.86



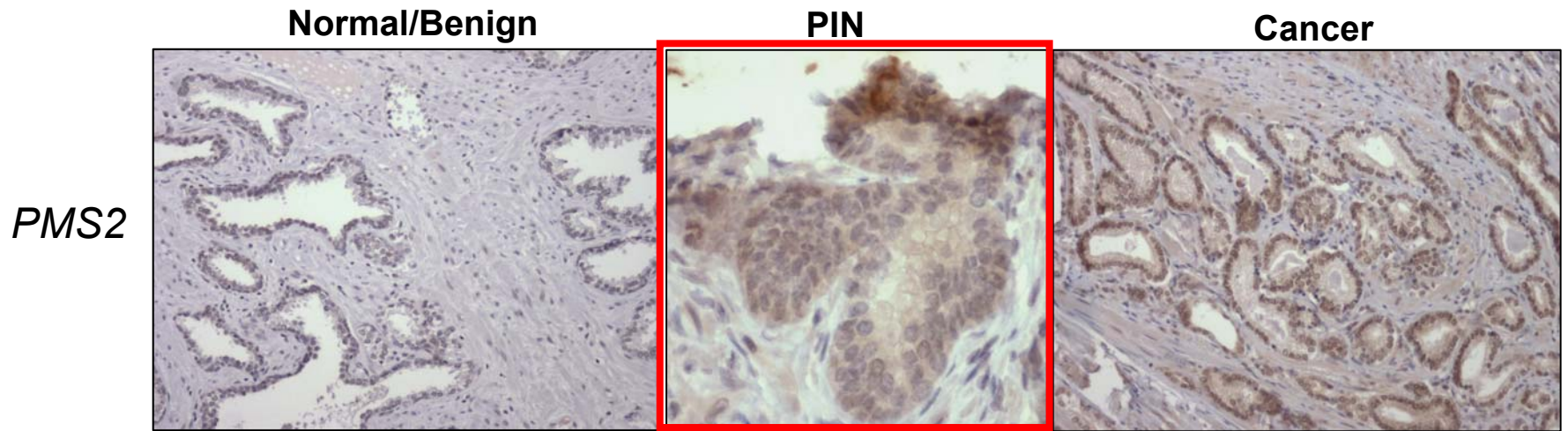
**PMS2 is significantly elevated in all Gleason grades of prostate cancer**

A. M. Norris, R. D. Woodruff, R. B. D'Agostino Jr., J. E. Clodfelter & Karin Drotschmann Scarpinato (2007).  
Elevated levels of the mismatch repair protein PMS2 are associated with prostate cancer. *Prostate*, 67, 214-225.

# Prostate Cancer Stages



# Prostate Cancer & Mismatch Repair



**PMS2 elevation is observed in premalignant lesions of the prostate:  
PIN**

# Microsatellite Instability

- Isolation of neoplastic prostate tissue by laser capture microscopy
- Determine microsatellite instability according to NCI guidelines (ABI)

## Microsatellite instability in mono- and dinucleotide runs of tissue with elevated PMS levels

MSI analysis	Elevation of	BAT25 mono	BAT26 mono	D2S123 di	D17S250 di	D5S346 di
MSI-H	PMS2	-	-	ND	+	+
MSI-H	PMS2	ND	-	+	+	-
MSI-H	PMS2	-	-	+	+	+
MSI-H	PMS2	+	-	-	+	+
no MSI	PMS+MLH1	-	-	-	-	-
<i>no MSI</i>	<i>none</i>	-	-	-	-	-



**PMS2 elevation is associated with microsatellite instability**

A. M. Norris, R. D. Woodruff, R. B. D'Agostino Jr., J. E. Clodfelter & Karin Drotschmann Scarpinato (2007).  
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# Summary

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1. **PMS2** is significantly **elevated** in prostate cancer.
2. PMS2 elevation is already observed **in premalignant prostate lesions**, suggesting that it is an early event in tumorigenesis.
3. PMS2 elevation is **independent of MLH1** expression.
4. PMS2 elevation causes **microsatellite instability**.
5. Microsatellite instability is ameliorated when **MLH1 is co-overexpressed**.
6. PMS2 elevation can be observed in **biopsy samples**, and in an **independent cohort** of patient samples.
7. PMS2 elevation increases **resistance to cytotoxic agents**.
8. PMS2 elevation provides a **growth advantage under oxidative stress**.



# Acknowledgement



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